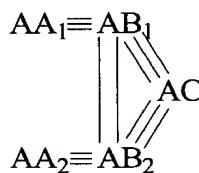


CLAIMS

1. A method of inhibiting osteoclastogenesis comprising the step of administering to a patient an amount of an inhibitor effective to inhibit osteoclastogenesis.

2. The method of claim 1 wherein the inhibitor has the formula:

5



wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF-R superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one 10 amide linkage is replaced with a substituted amide or an isostere of amide;

AB₁ is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB₂ and a third functional group capable of forming a covalent linkage with AA₁;

15 AB₂ is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB₁ and a third functional group capable of forming a covalent linkage with AA₂;

AA₁ is a moiety having hydrophobic properties and a functional group capable of 20 forming a covalent linkage with the third functional group of AB₂;

AA₂ is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB₂;

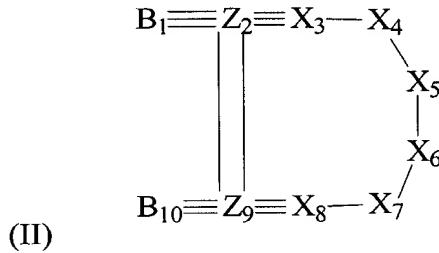
P. d 7/28/1999,

Inventors: Green, tall

Sub B1
“=” is a covalent linkage; and

“≡” is a covalent linkage.

3. The method of Claim 2 in which the amino acid substitutions are conservative.
4. The method of Claim 3 in which the member of TNF-R superfamily is TNF-R p55.
5. The method of Claim 4 wherein the inhibitor has the formula:



wherein:

B₁ and B₁₀ are each independently a peptide of 1-6 amino acids at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

10 Z₂ is a moiety that is capable of forming a covalent linkage with B₁, X₃ and Z₉;

Z₉ is a moiety that is capable of forming a covalent linkage with B₁₀, X₈ and Z₂;

X₃ is absent or a hydrophilic amino acid;

X₄ is a hydrophobic amino acid;

X₅ is a hydrophobic amino acid;

15 X₆ is a hydrophobic amino acid;

X₇ is a hydrophobic or hydrophilic amino acid;

X₈ is a hydrophobic or hydrophilic amino acid;

“-“ is an amide, substituted amide or an isostere of amide thereof;

“=” is a covalent linkage; and

20 “≡” is a covalent linkage.

6. The method of Claim 5, wherein:

B_1 and B_{10} are each independently a peptide of 1-2 amino acids, at least one of which is an aromatic amino acid;

Z_2 and Z_9 are each independently a Cys-like amino acid;

5 X_3 is absent or an acidic amino acid;

X_4 is an aromatic or apolar amino acid;

X_5 is a polar amino acid;

X_6 is a polar amino acid;

X_7 is an aromatic or polar amino acid;

10 X_8 is an aromatic, apolar or polar amino acid;

“-“ is an amide linkage;

“=“ is a disulfide linkage; and

“≡“ is an amide linkage.

Q. 15

The method of Claim 5, wherein:

15 B_1 and B_{10} are each independently Tyr or Phe;

Z_2 and Z_9 are each Cys;

X_3 is absent or Glu;

X_4 is Trp or Leu;

X_5 is Ser;

20 X_6 is Gln;

X_7 is Tyr or Asn;

X_8 is Tyr or Leu;

“-“ is an amide linkage;

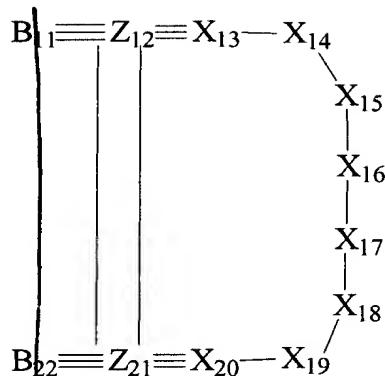
“=“ is a disulfide linkage; and

25 “≡“ is an amide linkage.

8. The method of Claim 7, wherein said inhibitor is selected from the group consisting of WP9Q - SEQ ID NO:13, WP9ELY - SEQ ID NO:12, WP9Y - SEQ ID NO:14, and WP9QY - SEQ ID NO:15.

Sub B3 9. The method of Claim 4, wherein the inhibitor has the formula:

(III)



wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

5 Z_{12} is a moiety that is capable of forming a covalent linkage with B_{11} , X_{13} and Z_{21} ;
 Z_{21} is a moiety that is capable of forming a covalent linkage with B_{22} , X_{20} and Z_{12} ;
 X_{13} is absent or hydrophobic amino acid;
 X_{14} is absent or hydrophilic amino acid;
 X_{15} is a hydrophilic or hydrophobic amino acid;
10 X_{16} is a hydrophilic amino acid;
 X_{17} is absent or a hydrophobic amino acid;
 X_{18} is a hydrophilic amino acid;
 X_{19} is a hydrophilic amino acid;
 X_{20} is a hydrophilic amino acid;
15 “-“ is an amide, a substituted amide or an isostere of amide thereof;
 “=“ is a covalent linkage; and
 “≡“ is a covalent linkage.

10. The method of Claim 9, wherein:

B_{11} and B_{22} are each independently a peptide of 1-3 amino acids, at least one of

20 which is an aromatic amino acid;

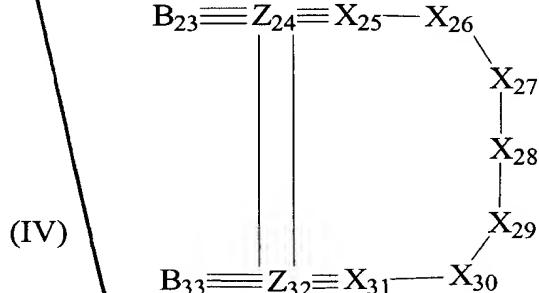
Z₁₂ and Z₂₁ are each independently a Cys-like amino acid;
X₁₃ is absent or an aromatic amino acid;
X₁₄ is absent or a polar amino acid;
X₁₅ is a basic, polar or apolar amino acid;
5 X₁₆ is a polar amino acid;
X₁₇ is absent or an apolar amino acid;
X₁₈ is an acidic amino acid;
X₁₉ is a polar amino acid;
X₂₀ is a basic amino acid;
10 “-“ is an amide linkage;
“=” is a disulfide linkage; and
“≡” is an amide linkage.

11. The method of Claim 10, wherein:
B₁₁ and B₂₂ are each independently Tyr or Phe;
15 Z₁₂ and Z₂₁ are each Cys;
X₁₃ is absent or Phe;
X₁₄ is absent or Thr;
X₁₅ is Ala, Asn or Arg;
X₁₆ is Ser;
20 X₁₇ is absent or Val;
X₁₈ is Glu;
X₁₉ is Asn;
X₂₀ is Arg or His;
“-“ is an amide linkage;
25 “=” is a disulfide linkage; and
“≡” is an amide linkage.

12. The method of Claim 11, wherein said inhibitor is selected from the group consisting of WP5 - SEQ ID NO:16, WP5N - SEQ ID NO:17, WP5R - SEQ ID NO:18, WP5J - SEQ ID NO:19, WP5JY - SEQ ID NO:20, WP5JN - SEQ ID NO:21, WP5JR -

SEQ ID NO:22, and WP5VR - SEQ ID NO:23.

13. The method of Claim 4, wherein the inhibitor has the formula:



wherein:

5 B_{23} and B_{33} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{24} is a moiety that is capable of forming a covalent linkage with B_{23} , X_{25} and Z_{32} ;

Z_{32} is a moiety that is capable of forming a covalent linkage with B_{33} , X_{31} and Z_{24} ;

X_{25} is absent or a hydrophilic amino acid;

10 X_{26} is a hydrophilic amino acid;

X_{27} is a hydrophilic amino acid;

X_{28} is a hydrophilic amino acid;

X_{29} is a hydrophilic amino acid;

X_{30} is absent or a hydrophilic amino acid;

15 X_{31} is absent or a hydrophilic amino acid;

 “-“ is an amide, a substituted amide or an isostere of amide;

 “≡” is a covalent linkage; and

 “≡” is a covalent linkage.

14. The method of Claim 13, wherein:

20 B_{23} and B_{33} are each independently a peptide of 1-3 amino acids, at least one of

which is an aromatic amino acid;

Z_{24} and Z_{32} are each independently a Cys-like amino acid;

X_{25} is absent or a basic amino acid;

X_{26} is a basic amino acid;

5 X_{27} is an acidic amino acid;

X_{28} is an apolar amino acid;

X_{29} is an apolar amino acid;

X_{30} is absent or a polar amino acid;

X_{31} is absent or an apolar amino acid;

10 “-“ is an amide linkage*

“=“ is a disulfide linkage; and

“≡“ is an amide linkage.

Sub B5 15. The method of Claim 14, wherein:

B_{23} and B_{33} are each independently Tyr or Phe;

15 Z_{24} and Z_{32} are each Cys;

X_{25} is absent or Arg;

X_{26} is Lys;

X_{27} is Glu;

X_{28} is Ieu, Pro or Met;

20 X_{29} is Gly;

X_{30} is absent or Gln;

X_{31} is absent or Val;

“-“ is an amide linkage;

“=“ is a disulfide linkage; and

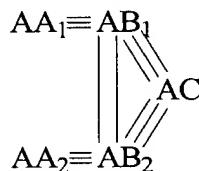
25 “≡“ is an amide linkage.

16. The method of Claim 15, wherein said inhibitor is selected from the group consisting of WP8L - SEQ ID NO:24, WP8JP - SEQ ID NO:25, WP8J - SEQ ID NO:26, and WP8JF - SEQ ID NO:27.

17. A method of treating patients who have diseases characterized by bone loss comprising the step of administering to said patient an amount of an inhibitor effective to inhibit such bone loss.

Sub B6 18. The method of claim 17 wherein said inhibitor is a compound having the formula:

5



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF- α superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one 10 amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB_2 and a third functional group capable of forming a covalent linkage with AA_1 ;

15 AB_2 is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB_1 and a third functional group capable of forming a covalent linkage with AA_2 ;

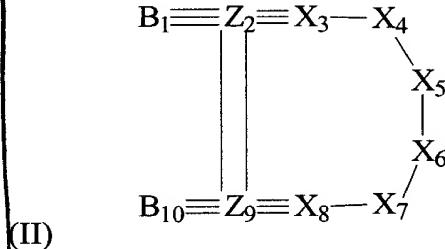
20 AA_1 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_1 ;

AA_2 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2 ;

“ \equiv ” is a covalent linkage; and

“ \equiv ” is a covalent linkage.

19. The method of claim 18 wherein the inhibitor has the formula:



wherein:

B_1 and B_{10} are each independently a peptide of 1-6 amino acids, at least one of

5 which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_2 is a moiety that is capable of forming a covalent linkage with B_1 , X_3 and Z_9 ;

Z_9 is a moiety that is capable of forming a covalent linkage with B_{10} , X_8 and Z_2 ;

X_3 is absent or a hydrophilic amino acid;

10 X_4 is a hydrophobic amino acid;

X_5 is a hydrophilic amino acid;

X_6 is a hydrophilic amino acid;

X_7 is a hydrophobic or hydrophilic amino acid;

X_8 is a hydrophobic or hydrophilic amino acid;

“-“ is an amide, substituted amide or an isostere of amide thereof;

15 “=“ is a covalent linkage; and

“ \equiv “ is a covalent linkage.

20. The method of claim 19 wherein:

B_1 and B_{10} are each independently a peptide of 1-3 amino acids, at least one of

which is an aromatic amino acid;

20 Z_2 and Z_9 are each independently a Cys-like amino acid;

X_3 is absent or an acidic amino acid;

X_4 is an aromatic or apolar amino acid;

X_5 is a polar amino acid;

X_6 is a polar amino acid;
 X_7 is an aromatic or polar amino acid;
 X_8 is an aromatic, apolar or polar amino acid;
“-“ is an amide linkage;
5 “=“ is a disulfide linkage; and
“≡“ is an amide linkage.

21. The method of claim 20 wherein:

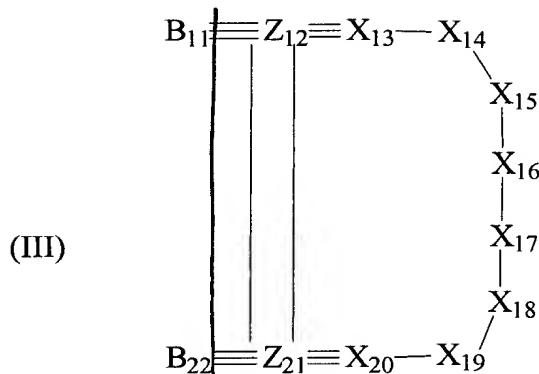
B_1 and B_{10} are each independently Tyr or Phe;
 Z_2 and Z_9 are each Cys;
10 X_3 is absent or Glu;
 X_4 is Trp or Leu;
 X_5 is Ser;
 X_6 is Gln;
 X_7 is Tyr or Asn;
15 X_8 is Tyr or Leu;
“-“ is an amide linkage;
“=“ is a disulfide linkage; and
“≡“ is an amide linkage.

22. The method of claim 18 wherein the compound is selected from the group

20 consisting of WP9Q - SEQ ID NO: 13, WP9ELY - SEQ ID NO: 12, WP9Y - SEQ ID NO: 14, and WP9QY - SEQ ID NO: 15.

Sub BT

23. The method of claim 18 wherein the inhibitor has the formula:



wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

5 Z_{12} is a moiety that is capable of forming a covalent linkage with B_{11} , X_{13} and Z_{21} ;

Z_{21} is a moiety that is capable of forming a covalent linkage with B_{22} , X_{20} and Z_{12} ;

X_{13} is absent or hydrophobic amino acid;

X_{14} is absent or a hydrophilic amino acid;

X_{15} is a hydrophilic or hydrophobic amino acid;

10 X_{16} is a hydrophilic amino acid;

X_{17} is absent or a hydrophobic amino acid;

X_{18} is a hydrophilic amino acid;

X_{19} is a hydrophilic amino acid;

X_{20} is a hydrophilic amino acid;

15 “-“ is an amide, a substituted amide or an isostere of amide thereof;

 “=“ is a covalent linkage; and

 “≡“ is a covalent linkage.

24. The method of claim 23 wherein:

B_{11} and B_{22} are each independently a peptide of 1-3 amino acids, at least one of

20 which is an aromatic amino acid;

Z_{12} and Z_{21} are each independently a Cys-like amino acid;
 X_{13} is absent or an aromatic amino acid;
 X_{14} is absent or a polar amino acid;
 X_{15} is a basic, polar or apolar amino acid;

5 X_{16} is a polar amino acid;
 X_{17} is absent or an apolar amino acid;
 X_{18} is an acidic amino acid;
 X_{19} is a polar amino acid;
 X_{20} is a basic amino acid;

10 “-“ is an amide linkage;
“=“ is a disulfide linkage; and
“≡“ is an amide linkage.

25. The method of claim 24 wherein:
 B_{11} and B_{22} are each independently Tyr or Phe;

15 Z_{12} and Z_{21} are each Cys;
 X_{13} is absent or Phe;
 X_{14} is absent or Thr;
 X_{15} is Ala, Asn or Arg;
 X_{16} is Ser;

20 X_{17} is absent or Val;
 X_{18} is Glu;
 X_{19} is Asn;
 X_{20} is Arg or His;
“-“ is an amide linkage;

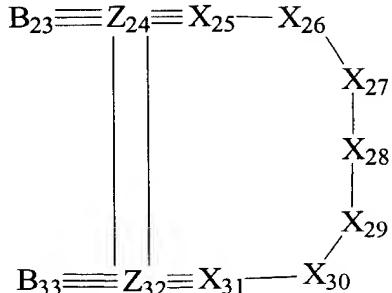
25 “=“ is a disulfide linkage; and
“≡“ is an amide linkage.

26. The method of claim 25 wherein the inhibitor is selected from the group consisting of WP5 - SEQ ID NO: 16, WP5N - SEQ ID NO: 17, WP5R - SEQ ID NO: 18, WP5J - SEQ ID NO: 19, WP5JY - SEQ ID NO: 20, WP5JN - SEQ ID NO: 21, WP5JR - SEQ ID

NO: 22, and WP5VR - SEQ ID NO: 23.

27. The method of claim 18 wherein the inhibitor has the formula:

Sub B8
(IV)



wherein:

5 B_{23} and B_{33} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{24} is a moiety that is capable of forming a covalent linkage with B_{23} , X_{25} and Z_{32} ;

Z_{32} is a moiety that is capable of forming a covalent linkage with B_{33} , X_{31} and Z_{24} ;

X_{25} is absent or a hydrophilic amino acid;

10 X_{26} is a hydrophilic amino acid;

X_{27} is a hydrophilic amino acid;

X_{28} is a hydrophobic amino acid;

X_{29} is a hydrophobic amino acid;

X_{30} is absent or a hydrophobic amino acid;

15 X_{31} is absent or a hydrophobic amino acid;

 “-“ is an amide, a substituted amide or an isostere of amide;

 “=” is a covalent linkage; and

 “ \equiv ” is a covalent linkage.

28. The method of claim 27 wherein:

20 B_{23} and B_{33} are each independently a peptide of 1-3 amino acids, at least one of

which is an aromatic amino acid;

Z_{24} and Z_{32} are each independently a Cys-like amino acid;

X_{25} is absent or a basic amino acid;

X_{26} is a basic amino acid;

5 X_{27} is an acidic amino acid'

X_{28} is an apolar amino acid;

X_{29} is an apolar amino acid;

X_{30} is absent or a polar amino acid;

X_{31} is absent or an apolar amino acid;

10 “-“ is an amide linkage;

“=“ is a disulfide linkage; and

“≡“ is an amide linkage.

29. The method of claim 28 wherein:

B_{23} and B_{33} are each independently Tyr or Phe;

15 Z_{24} and Z_{32} are each Cys;

X_{25} is absent or Arg;

X_{26} is Lys;

X_{27} is Glu;

X_{28} is Leu, Pro or Met;

20 X_{29} is Gly;

X_{30} is absent or Gln;

X_{31} is absent or Val;

“-“ is an amide linkage;

“=“ is a disulfide linkage; and

25 “≡“ is an amide linkage.

30. The method of claim 29 wherein the inhibitor is selected from the group consisting of WP8L - SEQ ID NO:24.

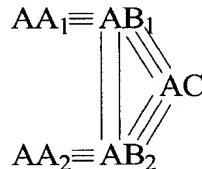
31. The method of claim 17 wherein the disease characterized by bone loss is selected

from the group consisting of osteoporosis, Paget's disease, metastatic bone disease, rheumatoid arthritis, and periodontal disease.

32. The method of claim 31 wherein the disease characterized by bone loss is osteoporosis.

5 33. A method of inhibiting bone resorption, comprising the step of administering to a patient an amount of an inhibitor effective to inhibit bone resorption.

Sub B8 34. The method of claim 33 wherein said inhibitor has the formula:



(I)

wherein:

10 AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF-R superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

15 AB₁ is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB₂ and a third functional group capable of forming a covalent linkage with AA₁;

20 AB₂ is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB₁ and a third functional group capable of forming a covalent linkage with AA₂;

Sub B9
AA₁ is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB₂;

AA₂ is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB₂;

5 “=” is a covalent linkage; and

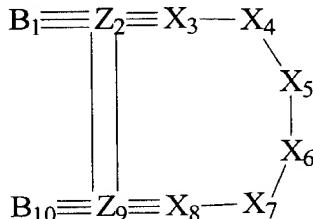
“≡” is a covalent linkage.

35. The method of Claim 34, in which the amino acid substitutions are conservative.

36. The method of ~~Claim 35~~ in which the member of TNF-R superfamily is TNF-R

p55.

Sub B10
37. The method of Claim 36, wherein the inhibitor has the formula:



wherein:

B₁ and B₁₀ are each independently a peptide of 1-6 amino acids at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

15 Z₂ is a moiety that is capable of forming a covalent linkage with B₁, X₃ and Z₉;

Z₉ is a moiety that is capable of forming a covalent linkage with B₁₀, X₈ and Z₂;

X₃ is absent or a hydrophilic amino acid;

X₄ is a hydrophobic amino acid;

X₅ is a hydrophobic amino acid;

20 X₆ is a hydrophobic amino acid;

X₇ is a hydrophobic or hydrophilic amino acid;

Sub BD 

X₈ is a hydrophobic or hydrophilic amino acid;
“-“ is an amide, substituted amide or an isostere of amide thereof;
“=” is a covalent linkage; and
“≡” is a covalent linkage.

5 38. The method of Claim 37, wherein:

B₁ and B₁₀ are each independently a peptide of 1-2 amino acids, at least one of which is an aromatic amino acid;

Z₂ and Z₉ are each independently a Cys-like amino acid;

X₃ is absent or an acidic amino acid;

10 X₄ is an aromatic or apolar amino acid;

X₅ is a polar amino acid;

X₆ is a polar amino acid;

X₇ is an aromatic or polar amino acid;

X₈ is an aromatic, apolar or polar amino acid;

15 “-“ is an amide linkage;

“=” is a disulfide linkage; and

“≡” is an amide linkage.

39. The method of Claim 38, wherein:

B₁ and B₁₀ are each independently Tyr or Phe;

20 Z₂ and Z₉ are each Cys;

X₃ is absent or Glu;

X₄ is Trp or Leu;

X₅ is Ser;

X₆ is Gln;

25 X₇ is Tyr or Asn;

X₈ is Tyr or Leu;

“-“ is an amide linkage;

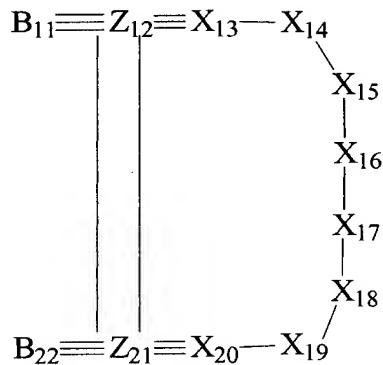
“=” is a disulfide linkage; and

“≡” is an amide linkage.

40. The method of Claim 39, wherein said inhibitor is selected from the group consisting of WP9Q - SEQ ID NO:13, WP9ELY - SEQ ID NO:12, WP9Y - SEQ ID NO:14, and WP9QY - SEQ ID NO:15.

Sub B11
41. The method of Claim 36, wherein the inhibitor has the formula:

5 (III)



wherein:

B₁₁ and B₂₂ are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z₁₂ is a moiety that is capable of forming a covalent linkage with B₁₁, X₁₃ and Z₂₁;

10 Z₂₁ is a moiety that is capable of forming a covalent linkage with B₂₂, X₂₀ and Z₁₂;

X₁₃ is absent or hydrophobic amino acid;

X₁₄ is absent or hydrophilic amino acid;

X₁₅ is a hydrophilic or hydrophobic amino acid;

X₁₆ is a hydrophilic amino acid;

15 X₁₇ is absent or a hydrophobic amino acid;

X₁₈ is a hydrophilic amino acid;

X₁₉ is a hydrophilic amino acid;

X₂₀ is a hydrophilic amino acid;

“-“ is an amide, a substituted amide or an isostere of amide thereof;

20 “=“ is a covalent linkage; and

Sub BII → “≡” is a covalent linkage.

42. The method of Claim 41, wherein:

B_{11} and B_{22} are each independently a peptide of 1-3 amino acids, at least one of which is an aromatic amino acid;

5 Z_{12} and Z_{21} are each independently a Cys-like amino acid;

X_{13} is absent or an aromatic amino acid;

X_{14} is absent or a polar amino acid;

X_{15} is a basic, polar or apolar amino acid;

X_{16} is a polar amino acid;

10 X_{17} is absent or an apolar amino acid;

X_{18} is an acidic amino acid;

X_{19} is a polar amino acid;

X_{20} is a basic amino acid;

“-“ is an amide linkage;

15 “=“ is a disulfide linkage; and

“≡” is an amide linkage.

43. The method of Claim 42, wherein:

B_{11} and B_{22} are each independently Tyr or Phe;

Z_{12} and Z_{21} are each Cys;

20 X_{13} is absent or Phe;

X_{14} is absent or Thr;

X_{15} is Ala, Asn or Arg;

X_{16} is Ser;

X_{17} is absent or Val;

25 X_{18} is Glu;

X_{19} is Asn;

X_{20} is Arg or His;

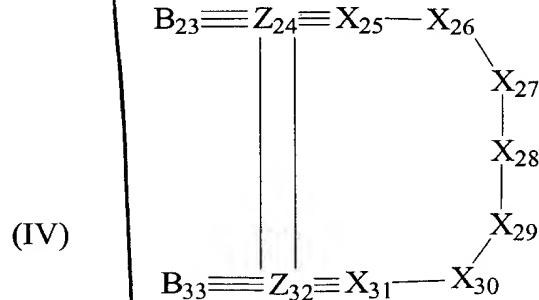
“-“ is an amide linkage;

“=“ is a disulfide linkage; and

“≡” is an amide linkage.

44. The method of Claim 43, wherein said inhibitor is selected from the group consisting of WP5 - SEQ ID NO:16, WPSN - SEQ ID NO:17, WP5R - SEQ ID NO:18, WP5J - SEQ ID NO:19, WP5JY - SEQ ID NO:20, WP5JN - SEQ ID NO:21, WP5JR - 5 SEQ ID NO:22, and WP5VR - SEQ ID NO:23.

Sub B12 45. The method of Claim 36, wherein the inhibitor has the formula:



wherein:

B_{23} and B_{33} are each independently a peptide of 1-6 amino acids, at least one of 10 which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{24} is a moiety that is capable of forming a covalent linkage with B_{23} , X_{25} and Z_{32} ;

Z_{32} is a moiety that is capable of forming a covalent linkage with B_{33} , X_{31} and Z_{24} ;

X_{25} is absent or a hydrophilic amino acid;

X_{26} is a hydrophilic amino acid;

15 X_{27} is a hydrophilic amino acid;

X_{28} is a hydrophilic amino acid;

X_{29} is a hydrophilic amino acid;

X_{30} is absent or a hydrophilic amino acid;

X_{31} is absent or a hydrophilic amino acid;

20 “-“ is an amide, a substituted amide or an isostere of amide;

“=” is a covalent linkage; and

“≡” is a covalent linkage.

46. The method of Claim 45, wherein:

B_{23} and B_{33} are each independently a peptide of 1-3 amino acids, at least one of

5 which is an aromatic amino acid;

Z_{24} and Z_{32} are each independently a Cys-like amino acid;

X_{25} is absent or a basic amino acid;

X_{26} is a basic amino acid;

X_{27} is an acidic amino acid;

10 X_{28} is an apolar amino acid;

X_{29} is an apolar amino acid;

X_{30} is absent or a polar amino acid;

X_{31} is absent or an apolar amino acid;

“-“ is an amide linkage’

15 “=” is a disulfide linkage; and

“≡” is an amide linkage.

47. The method of Claim 46, wherein:

B_{23} and B_{33} are each independently Tyr or Phe;

Z_{24} and Z_{32} are each Cys;

20 X_{25} is absent or Arg;

X_{26} is Lys;

X_{27} is Glu;

X_{28} is leu, Pro or Met;

X_{29} is Gly;

25 X_{30} is absent or Gln;

X_{31} is absent or Val;

“-“ is an amide linkage;

“=” is a disulfide linkage; and

“≡” is an amide linkage.

48. The method of Claim 47, wherein said inhibitor is selected from the group consisting of WP8L - SEQ ID NO:24, WP8JP - SEQ ID NO:25, WP8J - SEQ ID NO:26, and WP8JF - SEQ ID NO:27.